COA QUALIFICATION PLAN

The COA Qualification Plan (QP) should be accompanied by a cover letter and should include the following completed sections. This plan should contain the results of completed qualitative research and the proposed quantitative research plan. If literature is cited, please cite using the following formats:

- Using the number assigned to the source in a numbered reference list
- In-text with the source in an alphabetical reference list

Please do not leave any sections or subsections blank. If you do not have anything for that section or subsection, please explain the rationale (e.g., does not apply to this COA measure type). Even if the information was already included in a previous submission to the Agency, it should still be included in the QP. The QP is intended to be an organized, stand-alone submission package.

Note: Sections 1 and 2 will be posted publicly under Section 507. Sections 1-2 should be stand-alone sections; do not refer to or cross reference any appendices, attachments, or other QP sections. Section 507 refers to section 507 of the Federal Food, Drug, and Cosmetic Act [FD&C Act] which was created by Section 3011 of the 21st Century Cures Act.

Table of Contents

List QP sections, appendices and/or attachments along with the page numbers on which they begin. If multiple files are submitted, include an inventory document that lists each filename along with individual descriptions.

Section 1: Proposed Plan for COA Qualification

1.1 Introduction and overview

- Concise description of the disease and the clinical trial setting in which the planned or existing COA would be used.
- Limitations of existing assessments, brief description of the COA, and rationale for use in drug development.

1.2 Concept of interest for meaningful treatment benefit

- Describe the important aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use).

1.3 Context of use

- Targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups).

- Targeted study design; most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment.
- Targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve to support a primary or secondary efficacy endpoint.

1.4 Critical details of the COA, to the degree known

- Type of COA (e.g., patient-reported outcome [PRO]) and intended respondent(s), if applicable.
- Item content or description of the instrument (for existing instruments, provide the specific version of the instrument and a copy from which quantitative evidence has been or will be derived).
- Method of administration (i.e., self-administered, interview-administered, etc.).
- Mode of data collection (i.e., electronic, interactive voice response system, etc.).

1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortium).

Section 2: Executive Summary

High-level summary of what is included in this QP submission, including key results and brief descriptions of the sections below.

Section 3: Qualitative Evidence and Conceptual Framework

Summary of key evidence of content validity detailed within qualitative study reports (i.e., documentation that the COA measures the concept of interest in the context of use). Along with each study report, the associated study protocol should be provided.

3.1 Literature review (summary of literature and main conclusions from review). Append key publications that support instrument development in the proposed context use.

3.2 Expert input.

3.3 Respondent input (e.g., for PRO instruments, concept elicitation, focus groups, or in-depth qualitative interviews to generate items, response options, recall period, and finalize item content; for performance outcome [PerfO] instruments, evidence to support that the tasks being performed are representative of the specific health aspect of the concept of interest and are relevant to ability to function in day-to-day life).

3.4 Concept elicitation (e.g., concept saturation grid, summary of results, transcripts if available).

3.5 Item generation or task generation (for PerfO instruments), if applicable.

3.6 Cognitive interviews (e.g., summary of results from cognitive interview and usability testing if applicable, transcripts, if available).

3.7 Item finalization (e.g., item tracking matrix). Submit rationale and documentation for item selection, reduction, and/or modification (if any). This can be in a table or in descriptive text.

3.8 Draft conceptual framework (for existing instruments, the final conceptual framework), if applicable.

Sections 4, 5, and 6: Proposed Quantitative Analysis Plan

Include a statement confirming planned submission of datasets (patient-level data) and a data dictionary(s) with a future submission of a full qualification package (FQP). If the proposed COA relies on the development of a measurement system (e.g., an IRT-calibrated item bank), plan to provide the original calibration data and analysis plan so that we will be able to verify the item parameter estimates, as needed.

Section 4: Plan for Cross-sectional Evaluation of Measurement Properties

Submit a protocol for planned psychometric analyses that includes the elements outlined below.

Note: Include graphs to support the psychometric analyses, including line plots to support test-retest reliability, scatterplots to support all correlational analyses, and boxplots to support known groups validity analyses.

4.1 Study design and patient population.

4.1.1 Planned inclusion/exclusion criteria of planned study population.

4.1.2 Timing/schedule of planned assessments.

4.1.3 Sample size and justification (including sample size of subgroups and justification, if applicable).

4.1.4 Planned baseline demographic and clinical characteristics of study population.

4.2 Item level description

4.2.1 Planned item descriptive statistics, including frequency distribution of both item response and overall scores, evaluation of floor and ceiling effects, and percentage of missing response.

4.2.2 Planned inter-item, item-total relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework).

4.2.3 Plan for item inclusion and reduction decision-making, identification of subscales (if any), and modification to conceptual framework.

4.2.4 If the proposed COA relies on the development of a measurement system, the QP should include the analysis plan for the original item-level analysis (e.g., the IRT calibration process for a measurement system item bank). Likewise, with the FQP, provide the corresponding findings from the planned item-level analysis as applied to the submitted data referenced above.

4.3 Preliminary scoring algorithm (e.g., include information about evaluation of measurement model assumptions, applicable goodness-of-fit statistics).

4.3.1 Plan for handling missing data.

4.3.2 Plan for confirming scoring algorithm.

4.3.3 If the proposed COA relies on the development of a measurement system, plan to provide detailed information regarding scoring (i.e., full technical manual).

4.4 Reliability

4.4.1 Planned test-retest reliability analysis, if applicable (e.g., intraclass correlation coefficient).

4.4.2 Planned internal consistency reliability analysis, if applicable (e.g., Cronbach's alpha).

4.4.3 Planned intra- and inter-rater reliability analysis (e.g., kappa coefficient), if clinician-reported outcome (ClinRO) or intra-rater reliability if observer-reported outcome (ObsRO) instrument.

4.5 Construct Validity

4.5.1 Planned convergent and discriminant validity analysis (i.e., association with other instruments assessing similar or different concepts). Provide copies of the other administered instruments (and their scoring algorithms) and variable definitions and thresholds (or range).

4.5.2 Planned known-groups validity analysis (e.g., difference in scores between clinically distinct subgroups of subjects). Provide copies of the anchor scales and group definitions and thresholds (or range).

4.6 Score reliability in the presence of missing item-level and if applicable scale-level data (e.g., missing data simulation study).

4.7 Copy of instrument and any additional global scales proposed as anchors.

4.8 User manual and plans for further revision and refinement

4.8.1 Administration procedures.

4.8.2 Training administration.

4.8.3 Scoring and interpretation procedures.

Section 5: Longitudinal Evaluation of Measurement Properties (if a longitudinal study is planned)

5.1 Planned evaluation of the instrument's ability to detect change.

5.2 Copies of proposed anchor scales and thresholds.

Section 6: Interpretation of Score (if a longitudinal study is planned)

Planned evaluation and definition of meaningful within person change (improvement and worsening), including plans for including empirical cumulative distribution function (eCDF) and probability density function (PDF) curves (if applicable).

Section 7: Language Translation and Cultural Adaption (if applicable)

7.1 Process for simultaneous development of versions in multiple languages or cultures.

7.2 Process of translation/adaptation of original version.

7.3 Evidence that content validity is similar for versions in multiple languages.

Section 8: Questions to CDER

Section 9: References

9.1 List of references cited in QP.

9.2 Copies of the most important and relevant supportive literature.

Section 10: Appendices and Attachments

Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s)).

Revision History Date	Description of Changes
10.04.2021	Section 3.7: added to submit rationale and documentation for item selection, reduction, and/or modification (if any).
5.6.21	Edited Instructions: In-text with the source in an alphabetical reference list Added to Instructions: Even if the information was already included in a previous submission to the Agency, it should still be included in the QP. The QP is intended to be an organized, stand-alone submission package. Added a Table of Contents section along with description. Edited Section 3 introductory instructions.
3.26.21	Added that literature can be cited using in-text citations.
3.25.21	Added clarifications to the Proposed Quantitative Analysis Plan (Sections 4, 5, and 6) instructions for COAs that rely on the development of a measurement system. Added a note to Section 4 instructions. Added Sections 4.2.4 and 4.3.3. Clarified Sections 4.4.1 and 4.4.2 are only needed if applicable. In Section 4.4.3: added the text “intra- and” after the word planned, also added “intra-rater reliability” before observer reported. Section 4.5.2 added the term “clinically-distinct” to describe subgroups. Added an example to Section 4.6.
6.11.20	Added to Instructions: Please do not leave any sections or subsections blank. If you do not have anything for that section or subsection, please explain the rationale (e.g., does not apply to this COA measure type).
5.28.20	Initial version